Remarks

In accordance with the present invention, there are provided novel members of a new superfamily of receptor proteins which comprise three distinct domains: an extracellular, ligand-binding domain; a hydrophobic, trans-membrane domain; and an intracellular, receptor domain having serine kinase-like activity. Also provided are methods of screening compounds for binding to these receptors and bioassays for identifying agonists or antagonists for these receptors. Such compounds are useful, for example, for the therapeutic management of carcinogenesis, wound healing, and disorders of the immune, reproductive, or central nervous systems.

Claims 1-17 were pending before this communication. By this response, non-elected claims 1-10 and 14-17 have been canceled without prejudice, and claims 11-13 have been amended to define Applicant's invention with greater particularity by removing dependencies to cancelled claim 1. These amendments add no new matter and are fully supported by the specification and the original claims. Attached hereto is a marked-up version of the changes made to the claims, labeled APPENDIX A.

Therefore, claims 11-13 are currently pending. For the Examiner's convenience, a clean copy of the complete set of all pending claims for this application is also provided in APPENDIX B.

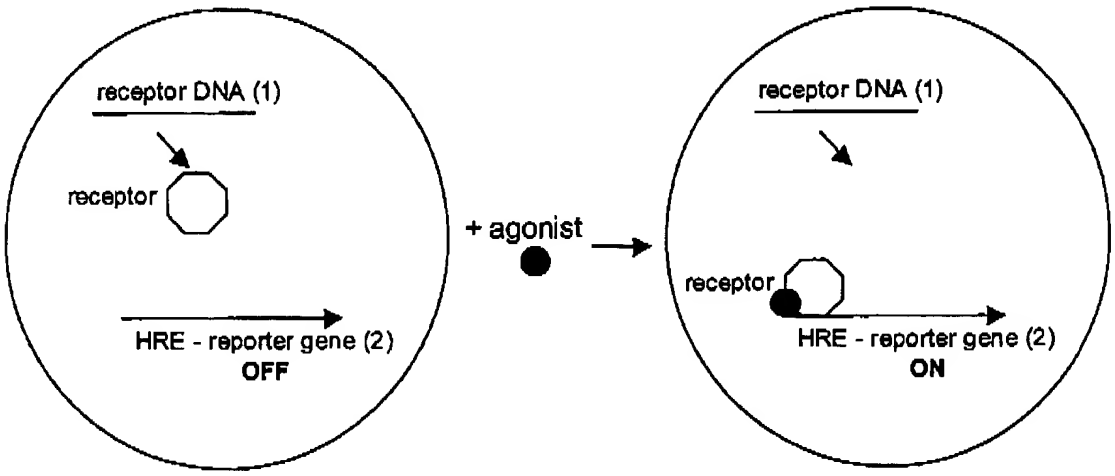
The restriction of claims 1-17 under 35 U.S.C. § 121, as allegedly being drawn to five distinct inventions, is respectfully traversed. However, in order to expedite prosecution and reduce the issues, the claims of Groups I, II and V (i.e., claims 1-10 and 14-17)have been cancelled.

Applicants respectfully submit that claim 11 (Group III), drawn to a cell-free method of screening compounds using invention receptors, could readily be combined and examined along with claims 12 and 13 (Group IV), drawn to cell-based bioassays to screen compounds using invention receptors, without adding to the burden on the Examiner. Groups III and IV are both

drawn to methods of using invention receptors to identify compounds which interact with the receptor, either physically (binding to the receptor) and/or functionally (modulating trans-activation activity of the receptor), and a prior art search of one group would, of necessity, involve a search of the other group.

Applicants respectfully disagree with the Examiner's assertion that "the method for screening compounds which bind to activin receptor proteins using a competitive binding assay will not provide . . . sufficient information on the identification of agonist/antagonists that modulate the transcription activation activity of the gene for activin receptor proteins" (emphasis added, see Office Action, Paper No. 8, at page 3, lines 9-13). Applicants respectfully submit that the Examiner has misconstrued the bioassays being claimed herein. Contrary to the Examiner's assertion, the agonist/antagonist modulates the transcription activity of the receptor itself.

The identification of agonist/antagonists is meant to define compounds which interact with the activin receptor protein, thereby modulating the function of the activin receptor as a transcriptional trans-activator. For example, with reference to the figure below, claim 12 is directed to a bioassay comprising cells which contain DNA expressing the receptor protein (1), and DNA encoding a hormone response element (HRE) recognized by the receptor protein, which is operatively linked to a reporter gene (2). Thus, if the cells are cultured with an agonist compound, the compound will bind to the receptor and trigger its ability to turn on expression of the reporter gene via the hormone response element.



Therefore, it is clear that a prerequisite for a compound to function as an agonist or antagonist is that it is capable of binding to the receptor, in order to modulate the function of the receptor. Accordingly, Applicants respectfully respect that Group III, the binding assay of claim 11, be rejoined with Group IV, the bioassay of claims 12 and 13, because compounds identified by the methods of claim 11 are clearly suitable for use in the other claimed methods as well.

Applicants further disagree with the Examiner's assertion that "the bioassay . . . will not be able to replace a competitive binding assay for screening activin receptor protein-binding compounds" (see Office Action, Paper No. 8, at page 3, lines 13-15). To the contrary, the specification clearly teaches that the binding assay can be used together with the bioassay in a screen of compounds. "Then, more detailed assays can be carried out with those compounds found to bind, to further determine whether such compounds act as agonists or antagonists of the invention receptors." See specification at page 18, lines 11-19. Thus, a thorough search of compounds that interact with invention receptors would of necessity uncover those which bind to the receptor, as well as those which modulate the function of the receptor as either agonists or antagonists.

Therefore, no conservation of PTO resources would be realized if the restriction requirement of Groups III and IV is maintained. Accordingly, reconsideration and withdrawal of this restriction requirement and regrouping of claims 11-13 into one group as argued above are respectfully requested.

However, in order to be fully responsive, Applicants elect Group III (i.e., claim 11) with traverse. Claims 12 and 13 are retained herein pending final disposition of the elected claim.

The further requirement for the election of a ***single*** amino acid sequence is respectfully traversed. Applicants respectfully submit that this requirement is improper and request that the Examiner reconsider and withdraw the requirement.

MPEP 803.04 provides that "[i]t has been determined that normally **ten** sequences constitute a reasonable number for examination purposes" (emphasis added). Applicants respectfully submit that limiting all applications to a single sequence is directly contrary to both the spirit and the text of the rules and is therefore improper. The present application provides **four** amino acid sequences that are all highly related, and a search of these sequences is reasonable and does not constitute an undue burden for examination.

Therefore, Applicants respectfully request that the Examiner follow the required restriction practice in accordance with the MPEP, and withdraw the present request to limit examination in this application to a single amino acid sequence because a search of all four sequences present does not constitute an undue burden on the office.

However, in order to be fully responsive, Applicants elect SEQ ID NO: 2', the human activin receptor protein amino acid sequence, with traverse. All of claims 11-13 read on this sequence.

Conclusion

In view of the above amendment and remarks, reconsideration of the restriction requirement, and prompt and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Enclosures: Appendices A and B

APPENDIX A – ALTERED CLAIMS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 11-13 have been amended as follows:

11. (Amended) A method for screening a collection of compounds to determine those compounds which bind to receptors of the activin/TGF-β superfamily, said method comprising employing **a** [~~the~~] receptor [~~of claim 1~~] in a competitive binding assay,

wherein said receptor is a novel receptor protein characterized by having the following domains, reading from the N-terminal end of said protein:

an extracellular, ligand-binding domain,

a hydrophobic, trans-membrane domain, and

an intracellular, receptor domain having serine kinase-like activity.

12. (Amended) A bioassay for evaluating whether compounds are agonists for **a** receptor protein(s) [~~according to Claim 1~~], or functional modified forms of said receptor protein(s), said bioassay comprising:

(a) culturing cells containing:

DNA which expresses said receptor protein(s) or functional modified forms of said receptor protein(s), and

DNA encoding a hormone response element operatively linked to a reporter gene,

wherein said culturing is carried out in the presence of at least one compound whose ability to induce transcription activation activity of said receptor protein is sought to be determined; and thereafter

(b) monitoring said cells for expression of said reporter gene,

wherein said receptor protein(s) is a novel receptor protein characterized by having the following domains, reading from the N-terminal end of said protein(s):

an extracellular, ligand-binding domain,

a hydrophobic, trans-membrane domain, and

an intracellular, receptor domain having serine kinase-like activity.

13. (Amended) A bioassay for evaluating whether compounds are antagonists for a receptor protein(s) [~~according to Claim 1~~], or functional modified forms of said receptor protein(s), said bioassay comprising:

(a) culturing cells containing:

DNA which expresses said receptor protein(s) or functional modified forms of said receptor protein(s), and

DNA encoding a hormone response element operatively linked to a reporter gene,

wherein said culturing is carried out in the presence of:

increasing concentrations of at least one compound whose ability to inhibit transcription activation of said receptor protein(s) is sought to be determined, and

a fixed concentration of at least one agonist for said receptor protein(s), or functional modified forms of said receptor protein(s); and thereafter

(b) monitoring in said cells the level of expression of the product of said reporter gene as a function of the concentration of said compound, thereby indicating the ability of said compound to inhibit activation of transcription,

wherein said receptor protein(s) is a novel receptor protein characterized by having the following domains, reading from the N-terminal end of said protein(s):

an extracellular, ligand-binding domain,

a hydrophobic, trans-membrane domain, and

an intracellular, receptor domain having serine kinase-like activity.

APPENDIX B – COMPLETE SET OF PENDING CLAIMS

11. (Amended) A method for screening a collection of compounds to determine those compounds which bind to receptors of the activin/TGF-β superfamily, said method comprising employing a receptor in a competitive binding assay,

wherein said receptor is a novel receptor protein characterized by having the following domains, reading from the N-terminal end of said protein:

an extracellular, ligand-binding domain,

a hydrophobic, trans-membrane domain, and

an intracellular, receptor domain having serine kinase-like activity.

12. (Amended) A bioassay for evaluating whether compounds are agonists for a receptor protein(s), or functional modified forms of said receptor protein(s), said bioassay comprising:

(a) culturing cells containing:

DNA which expresses said receptor protein(s) or functional modified forms of said receptor protein(s), and

DNA encoding a hormone response element operatively linked to a reporter gene,

wherein said culturing is carried out in the presence of at least one compound whose ability to induce transcription activation activity of said receptor protein is sought to be determined; and thereafter

(b) monitoring said cells for expression of said reporter gene,

wherein said receptor protein(s) is a novel receptor protein characterized by having the following domains, reading from the N-terminal end of said protein(s):

an extracellular, ligand-binding domain,

a hydrophobic, trans-membrane domain, and

an intracellular, receptor domain having serine kinase-like activity.

13. (Amended) A bioassay for evaluating whether compounds are antagonists for a receptor protein(s), or functional modified forms of said receptor protein(s), said bioassay comprising:

(a) culturing cells containing:

DNA which expresses said receptor protein(s) or functional modified forms of said receptor protein(s), and

DNA encoding a hormone response element operatively linked to a reporter gene,

wherein said culturing is carried out in the presence of:

increasing concentrations of at least one compound whose ability to inhibit transcription activation of said receptor protein(s) is sought to be determined, and

a fixed concentration of at least one agonist for said receptor protein(s), or functional modified forms of said receptor protein(s); and thereafter

(b) monitoring in said cells the level of expression of the product of said reporter gene as a function of the concentration of said compound, thereby indicating the ability of said compound to inhibit activation of transcription,

wherein said receptor protein(s) is a novel receptor protein characterized by having the following domains, reading from the N-terminal end of said protein(s):

an extracellular, ligand-binding domain,

a hydrophobic, trans-membrane domain, and

an intracellular, receptor domain having serine kinase-like activity.